Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-131 are pending in this application and are rejected on various grounds. Claims 119-124 have been amended with a functional recitation: "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" and for clarity. Further, all pending claims have been amended to remove references to "Figures". Claim 128 has been canceled without prejudice or disclaimer. The rejections to the presently pending claims are respectfully traversed.

Priority

Applicants rely on the 'Gene amplification' assay for patentable utility of this case, first disclosed in International Application PCT/US/00/03565, filed February 11, 2000, priority for which has been claimed in this application. Applicants further submit that the subject matter defined in that application provides a specific and substantial asserted utility or a well established utility for the claimed invention for the same reasons as those discussed below under the utility section for the present application. Hence, the present application is at least entitled to an effective filing date of **February 11, 2000.**

Information disclosure Statement

The Examiner had objected to the previously submitted IDS because it did not comply with the requirements of 37 C.F.R. § 1.98(a)(2). Applicants hereby submit a new IDS separately enlisting each accession number for the sequence, the reference and the database where the sequence is available, from the previously filed Blast report of 5/31/2002 which complies with 37 C.F.R. § 1.98(a)(2). Consideration of this Information Disclosure Statement is respectfully requested.

Specification

The disclosure has been amended to delete all "embedded hyperlink and/or other form of browser-executable code." Accordingly, Applicants believe that all objections to the specification have been overcome.

Claim Rejections – 35 USC § 101 and § 112, first paragaraph

A. Claims 119-131 are rejected under 35 U.S.C. §101 allegedly because "the because the claimed invention is not supported by a specific, substantial and credible asserted utility or well established utility."

B. Claims 119-131 were rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a substantially asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention."

Regarding the gene amplification data, the Examiner says that the specification does not describe the significance of the expression of genes encoding PRO1245, nor does it compare the expression of the PRO1245 polypeptide in normal lung and colon tissues to that of the expression of lung and colon tumors. The Examiner further asserts that the specification establishes no connection between the expression of PRO1245 and developing lung or colon tumors. For the reasons outlined below, Applicants respectfully disagree.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any

reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: **"If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."**

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Arguments

Claim 128 has been canceled. Applicants respectfully disagree with and traverse the rejection to the remaining claims.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants submit exemplary articles to show that the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and Cell. Proteomics, 2002,

Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in

approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1245 gene, that the PRO1245 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1245 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Assuming *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which the Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant

> information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1245 polypeptide, for example, in detecting over-expression or absence of expression of PRO1245. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

Hence, these data clearly support a role for PRO1245 as a lung or colon tumor marker. Thus, Applicants request that the present 35 U.S.C. §101 and §112, first paragraph rejections to the pending claims be withdrawn.

Claim Rejections - 35 USC § 112, first paragraph -written description

Claims 119-131 are rejected under 35 U.S.C. 112, first paragraph because allegedly, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

The Legal standard for Written Description

The well- established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *In re* Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F. 2d at 1563, 19 USPQ2d at 1116 (Fed. cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. see e.g.Vas-Cath, Inc. v. Mahurkar, 935 F. 2d at 1563, 19 USPQ2d at 1116 (Fed. cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F. 3d 989, 996 (Fed. Cir. 2000).

Arguments

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The instant invention, defined by the claims, concerns

polypeptides having 80%, 85%, 90%, 95% or 99% sequence identity with the disclosed polypeptide sequence SEQ ID NO: 408 and further, with the functional recitation: "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors." Specific utility has been asserted in the present invention based on the amplification the nucleic acids encoding PRO1245 and the pending claims recite this functional feature. Thus, the pending claims are drawn to a genus of polypeptides defined both by sequence and functional identity. It would have been obvious to one skilled in the art at the effective priority date, in view of Applicant's possession of the PRO1245 sequence (SEQ ID NO: 408), that the Applicant possessed obvious variations and adaptations of SEQ ID NO: 408 as well, at the time of filing. Based on the detailed description of the cloning and expression of variants of PRO1245 in the specification, the description of the gene amplification assay and description of testing the ability of test variant polypeptides in the assay, the actual reduction to practice of sequence SEQ ID NO: 408 and the knowledge in the art, Applicants submit that one of skilled in the art would know that Applicants possessed the invention as claimed in the instant claims.

Hence, Applicants request that the present rejection to the present claims be reconsidered and withdrawn.

Claim Rejections – 35 USC § 102

a. Claims 119-131 are rejected under 35 U.S.C. §102(b) as being anticipated by as being anticipated by WO 99/63088, dated December/1999; WO 99/60160, dated November/1999; WO 00/00610, dated June/2000.

Based on the discussions above, Applicants believe that they are entitled to at least an effective date of **February 11, 2000** for this application. Accordingly, WO 99/63088, dated December/1999 and WO 99/60160, dated November/1999 are **102(a)** art instead. Applicants submit that WO 99/63088, dated December/1999 is the Applicants own art and can be overcome with an affidavit if necessary. Further, Applicants submit that the nucleic acids and polypeptides of SEQ ID NO: 407 and 408 were cloned, sequenced and disclosed in U.S. provisional application 60/097978, filed 8/26/1998 as SEQ ID NOs: 2 and 1 (Figures 2 and 1) and priority has been claimed to this provisional application in this application as well. Hence, the Applicants invention of PRO1245 and its encoding nucleic acids predate the WO 99/60160, dated

November/1999 reference as well. If necessary, a Declaration can be submitted to reiterate this point.

Accordingly, Applicants submit that the above cited art are not prior art and this rejection should be withdrawn.

b. Claims 119-125 and 129 are rejected under 35 U.S.C. §102(a) as being anticipated by Krop *et al.*, dated (August/2001).

Based on the discussions above, Applicants believe that they are entitled to at least an effective date of **February 11, 2000** for this application. Accordingly, the above cited reference is not prior art and this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C44). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 13, 2004

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